REMARKS

The Office Action and the cited and applied references have been carefully studied. No claim is allowed. Claims 1, 16, 19, 21, 24, 25-34, 44, 45, and 52-54 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1 and 52 have been objected to because of informalities. Appropriate correction is made to claim 1, thereby obviating this objection with respect to claim. Claim 52 presently appears merely for the purpose of having a claim directed to the non-elected inventions in a single claim for purposes of filing a divisional application at a later date.

Claims 1, 15, 16, 19-34 44, 45, and 52 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendment to the claims. It is now clear from amended claim 16 that the examiner's assumption that the claim is drawn to a peptide consisting of SEQ ID NOs: 35, 36, 37, 38, 39, 40, or 41 is correct.

Claims 22 and 23 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention. The rejected claims are drawn to a Lactadherin-derived peptide with a non-natural modification, which renders the modified peptide more immunogenic or more stable than the unmodified peptide. This rejection is respectfully traversed.

While claim 22 is now cancelled without prejudice, claims 21 and 23 which recite non-natural modifications, such as peptide bond modifications disclosed on page 17, lines 27-29, with lines 30-33 incorporating by reference a well-known reference on preparing peptidomimetic compounds. The paragraph bridging pages 17-18; page 18, lines 17-18; paragraph bridging pages 18-19; page 19, lines 12-25; and page 20, lines 5-19, disclose further non-natural modifications and non-natural amino acids. Accordingly, "non-natural modification" as recited in claims 21 and 23 is indeed adequately described in the specification as originally filed.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 26-29 and 32-34 have been rejected under 35 U.S.C. §112, first paragraph, for lack of written description. The examiner states that the specification does not teach any Lactadherin-derived peptide effective to inhibit cancer or cancer metastases. This rejection is respectfully traversed.

Example 3 on pages 38-40 of the specification discloses results with seven 9-mer tumor associated antigen peptides (Table 7) predicted to bind with high affinity to HLA-A2. All peptides bound well to the HhD molecules expressed on RMA-S transfectant (Fig. 13), demonstrating stabilization of cell surface HhD on RMA-S cells by Lactadherin (BA-46). Fig. 14 shows the immunogenicity of BA-46 peptides (anti-BA-46 peptide CTL activity) in HhD mice and Fig. 15 shows lysis of BA-46 peptide loaded targets by CTL induced against breast carcinoma extracted peptides in HhD mice. In Fig. 16, CTL against individual BA-46 peptides showed 30-50%

higher activity against breast tumor extract versus normal breast loaded target cells, supporting preferential CTL activity against breast tumor TAAs. HLA-A2.1 (HhD) restricted lysis of a breast carcinoma cell line by CTL induced against BA-46 derived peptides or tumor extracted peptides is shown in Fig. 17, where the BA-46 derived peptides preferentially lysed a breast carcinoma line-HhD transfectant relative to parental cells. Accordingly, based on the disclosure in the present specification, those of skill in the art would recognize that applicant was in possession of the claimed invention. Attached hereto are applicants' own publication, Carmon et al., J. Clin. Invest. 110(4):453-462 (2002), and an editorial from the same issue of the journal (page 423), which provide further evidence that BA-46 (Lactadherin) derived peptides are processed and presented by human breast carcinoma cells and that adoptive transfer of HhD-derived bulk CTLs to nude mice bearing human breast carcinoma transplants reduced tumor growth (see abstract), as would be expected by those of skill in the art based on the disclosures and teachings in the instant specification.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 15, 16, 19-34, 44, 45, and 52 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The examiner indicates that the claims are drawn to Lactadherin-derived peptides and pharmaceutical or

vaccine composition comprising a Lactadherin-derived peptides and pharmaceutical or vaccine composition comprising a Lactadherin-derived peptide. The examiner states that, since the specification mostly talks about generating cytotoxic T lymphocytes (CTLs) directed against tumor associated antigen (TAA) derived peptides presented by MHC molecules, the claims are interpreted as drawn to Lactadherin derived peptides that induce CTLs for treating breast cancer cells and this rejection has several aspects. It is the examiner's position that the instant specification does not disclose that SEQ ID NOs:35-41 or any other Lactadherin derived peptide could be used as antigenic peptide to produce CTLs *in vivo* or even *in vitro*. The examiner further holds that the specification does not provide any direct data that a peptide or any other variants derived from Lactadherin actually produce CTLs which target any tumor cells. The examiner asserts that the CTLs in Figures 14-16 are generated with tumor extracts, not by Lactadherin peptides. This rejection is respectfully traversed.

Contrary to the examiner's assertions, Figs. 14 and 15 do indeed show CTLs generated from Lactadherin peptides. In the brief description of the drawings for Fig. 14 and 16 on pages 10-11 of the specification, it is disclosed that mice were immunized with RMA-S-HhD-B7.1 cells loaded with BA-46 peptides as described in the Materials and Methods. Page 25 of the specification presents the Materials and Methods for vaccination where peptide-loaded RMAOS-HdD-B7.1 cells were injected into mice. CTLs generated in these mice were then used in *in vitro* cytotoxicity

assays, where lysis of tumor extracted peptide loaded target cells by the CTLs was demonstrated.

Much of the results presented for BA-46 (Lactadherin) peptides in Figs. 13-17 are also presented in the Carmon et al. (2002) publication attached hereto. The same BA-46 derived peptides disclosed in the present specification are reported to contain the motif recognized by the MHC class I molecule HLA-A21 and that are processed and presented by human breast carcinoma cells (abstract). In addition, adoptive transfer of HhD-derived bulk CTLs (generated by vaccinating HhD mice with BA-46 derived peptides individually loaded on FMA-S-HhD-B7 cells) to nude mice bearing human breast carcinoma transplants reduced tumor growth *in vivo* (abstract; page 459, middle of left column). Furthermore, PBLs derived from breast carcinoma patients show epitope specific and HLA-A2.1 restricted cytotoxic activity upon stimulation with BA-46 peptides (paragraph bridging pages 459 and 460). Accordingly, it would be well appreciated in the art, given the disclosure and guidance in the specification and particularly the use of peptide-loaded cells, such as the peptide-loaded antigen presenting cells of the elected species, that the presently claimed invention is fully enabling to those of skill in the art. If the examiner deems it necessary to present the results in Carmon et al. (2002) in declaration form, the examiner is requested to advise applicants and they will proceed to present the results in declaration form.

The examiner's attention is further directed to page 460, right column, of the attached Carmon et al. (2002) reference, where it is disclosed:

> BA46 appears to belong to group 5 of tumor antigens, although it was earlier reported as expressed in lactating breast and in breast and ovarian tumors only (8, 14). However, we show that BA46 expression is not limited to breast and ovarian carcinomas, but expression is detected in transitional cell carcinomas of bladder and colon cancers as well, similar to the epithelial TAA MUC1.

Accordingly, use of BA-46 TAA peptides is not limited to only breast cancer.

The remainder of the rejection is summarized by the examiner taking the position that:

> It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer.

In MPEP 2107.01 (IV) on the relationship between 35 U.S.C. 112, first paragraph, and 35 U.S.C. 101, it states:

> It is equally clear that a rejection based on "lack of utility", whether grounded upon 35 U.S.C. 101 or 35 U.S.C. 112, first paragraph, rests on the same basis (i.e., the asserted utility is not credible)..... In other words, Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper.

Also in MPEP 2107.01, but in section III on therapeutic or pharmacological utility, it states:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Scott [v. Finney], 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed. Cir. 1994)]. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, <u>necessarily includes the expectation of further search and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.</u> Were we to require Phase II testing in order to prove utility, the associated

> costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. (emphasis added)

Given the results shown in Example 3 and the disclosures and teachings in the present specification as a whole, one of skill in the art would accept applicants' assertion that the presently claimed peptide would be useful for treating cancer. A copy of an editorial appearing in the same issue of J. Clin. Invest. 110(4):423 (2002) as the Carmen et al. (2002) publication is attached hereto to show that certainly at least the editors of the journal found it credible that the Lactadherin peptides presently claimed are potential peptide vaccines for breast cancer.

The present invention is enabled and withdrawal of this rejection is in order. Reconsideration and withdrawal of the rejection are respectfully requested.

The examiner states that if applicants could overcome the above §112, first paragraph rejections, claims 1, 15, 16, 19-34, 44, 45, and 52 are still rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for SEQ ID NOs:35-41 being able to complex with HLA-A2, does not reasonably provide enablement for any Lactadherin-derived peptide fragments capable of specifically being associated with any other MHC molecule. This rejection is respectfully traversed.

Regarding the examiner's statement that the rejected claims encompass any peptide fragment from SEQ ID NO:2 being used as an immunogen, wherein said CTLs specifically target breast

cells, amended claim 1 is now directed to only a nona- or decapeptide appearing in the sequence of Lactadherin, which peptide is selected so as to promote effective binding to a MHC Class 1 type molecule so as to elicit a CTL response. In Example 3, at the bottom of page 38, it is disclosed that the amino acid sequence of human BA-46 was screened for HLA-A2 binding motifs by a HLA binding motif program (see also the last paragraph of page 24 on scoring of HLA-A2.1 peptides). Thus, the BA-46 peptides of Table 7 on page 39 are only seven of the highest scoring 9-mer peptides predicted to bind with high affinity to HLA-A2. As can be seen from the results with the highest scoring BA-46 peptides in Example 3 and in the Carmon et al (2002) publication attached hereto, the scoring of a HLA peptide binding prediction software, in which the theoretical binding scores represent calculated half-life of the HLA-A2.1-peptide complex, is quite correlative as a group to what is observed in the CTL response elicited. Other peptides with lower affinity for HLA-A2.1 can also be predicted by the same software and can be synthesized for possible use in the present invention. Based on what was found with TAA peptides from Lactadherin restricted to HLA-A2.1, one of skill in the art is enabled to use available information on HLA peptide binding motifs and other available HLA peptide binding prediction software to identify TAA peptides from Lactadherin which are restricted to other HLA molecules. Accordingly, the present claims are enabled for the scope claimed.

Reconsideration and withdrawal are therefore respectfully requested.

Claims 1, 15, 19, 20, 44, and 52 have been rejected under 35 U.S.C. §102(b) as being anticipated by any of U.S. Patent 5,455,031, WO 95/15171, or Larocca et al. (Cancer Res. 51:4994-4998, 1991). The examiner states that the claims are drawn to Lactadherin-derived peptides *per se* comprising 8-10 amino acid residues which the examiner indicates would read on the protein sequences disclosed in the applied references.

This rejection is obviated by the amendment to the claims to recite a nona or decapeptide, which clearly would not read on the full length (i.e, 46 kDa) protein disclosed in the references relied upon by the examiner. Accordingly, the cited and applied references cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
ALLEN C. YUN
Registration No. 37,971

ACY:pp
624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\Y\YEDA\Eisenbach3\PTO\amendmentB.doc